Ineffective Therapy, Underpowered Studies, or Merely Too Little, Too Late?

Risk Factors and Impact of Maternal Corticosteroid Treatment on Outcome in Antibody-Associated Fetal Heart Block

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It is estimated that 2% to 3% of pregnant women carry the anti-SSA/Ro antibody, which can be found in various autoimmune disorders, including Sjögren syndrome (SS), systemic lupus erythematosus, rheumatoid arthritis, and mixed connective tissue disorder. In addition, many women are asymptomatic carriers, with less than one third of anti-SSA/Ro-positive women diagnosed with a rheumatological disorder preceding the discovery of advanced heart block in the fetus. Prospective studies have demonstrated that, in the absence of a previously affected pregnancy, the fetuses of these women bear up to a 3% risk of developing cardiac manifestations of neonatal lupus (NL), including cardiac conduction abnormalities, structural cardiac defects, and isolated cardiomyopathies. In women with a previously affected pregnancy, the recurrence rate of congenital heart block can reach as high as 17%.

The cardiac conduction manifestations of NL are thought to result from a pathological response to the transplacental acquisition of anti-SSA/Ro whereby an immune-mediated inflammatory pathway triggers injury and eventually fibrosis of the atrioventricular (AV) node. In addition, anti-SSA/Ro antibodies appear to inhibit activation of the cardiac L-type calcium channels, which are essential to normal AV node conduction. The role of anti-SSB/La antibodies is less clearly defined. Although anti-SSB/La alone has not been associated with conduction abnormalities, some evidence suggests that it may potentiate the effects of anti-SSA/Ro-mediated injury.

Antibody-exposed infants without cardiac involvement at birth have little risk of later developing AV block; however, complete AV block can evolve in fetuses with second-degree AV block in utero or neonates born with first- or second-degree AV block. Jaeggi and colleagues reported that the timing of initial presentation of complete AV block correlated with mortality. Among the 29 cases diagnosed in utero, there was a 43% total mortality, including 6 intrauterine deaths and 6 within the first week of life. However, among the 33 cases diagnosed postnatally, there was only a 6% mortality rate with no deaths in the neonatal period. Among those who survived, nearly 90% ultimately required a pacemaker. Though there have been prior studies evaluating the cardiac-related morbidity and mortality of NL, these have shown vastly different results relative to frequency of pacemaker implantation and overall survival. Interpretation of such variability is complicated by inconsistent inclusion criteria relative to maternal antibody status, cohort size, and significant disparity in glucocorticoid treatment strategies. Even with decades of experience and an in-depth understanding of the relationship between fetal anti-SSA/Ro exposure and heart block, the medical community has currently not reached a consensus on the indications, dosage, or appropriate use of corticosteroid therapy.

Despite our knowledge of who is at risk for developing the cardiac manifestations of NL and what that risk entails, many questions still surround the monitoring and prenatal management of pregnant women with anti-SSA/Ro antibodies. When should monitoring begin? What should it consist of and how often should it occur? When should it stop? What can be done when an abnormality in fetal cardiac conduction is identified? Finally, how can we best counsel these women and their partners on risk of exposure to maternal anti-SSA/Ro? Two multicenter articles in the current issue of Circulation, Eliasson et al and Izmirly et al, attempt to answer some of these questions.

Eliasson and colleagues report a retrospective, multinational (from Europe and Brazil), multicenter study of 175 patients diagnosed with second- or third-degree AV block in utero. The objectives of the study were to identify risk factors associated with increased mortality in these individuals and to evaluate current clinical practice and the influence of maternal steroid administration on fetal outcome. Of the 162 pregnancies in which antibody status was available, 80% showed AV block associated with maternal anti-SSA/Ro antibodies. Overall, 91% survived throughout gestation; of those, 93% survived the neonatal period. Maternal fluorinated corticosteroid administration occurred in 38% of pregnancies. Fetal and neonatal mortality were not impacted by steroid administration or the presence of maternal anti-SSA/Ro. In addition, there was no significant difference between the cohorts of steroid-treated and untreated subjects with regard to echocardiographic findings, such as left ventricular systolic...
function, the presence of hydrops fetalis, ventricular rate, and incomplete AV block. There was, however, significant variability in use of maternal steroids between centers. Clinical parameters associated with an increase in mortality were: gestational age <20 weeks at diagnosis, ventricular rate <50 bpm, hydrops fetalis, and impaired left ventricular systolic function. Surprisingly, except for lower gestational age at time of diagnosis in the treated group, the incidence of these risk factors was found to be similar in both the steroid-treated and untreated cohorts.

The study by Eliasson and colleagues highlights both the significant practice variability between centers with regard to which patients receive steroids and the unexpected lack of correlation between echocardiographic markers of fetal wellness and maternal steroid administration. In addition, as the authors point out, these results contrast with those of Jaeggi and colleagues, who demonstrated a lower mortality rate in those treated with maternal steroid administration compared with historical controls. However, the historical controls of Jaeggi et al had more of the risk factors for increased mortality identified by Eliasson and colleagues compared with the steroid-treatment group. Of note, Friedman and colleagues reported that there was no relationship evident between maternal steroid treatment and improvement in second-degree AV block or other clinical parameters. Even in fetuses with multiple identified risk factors, there was no survival benefit in the steroid-treated group. However, again, because there was significant variability in steroid use and the specific details of steroid therapy, it remains difficult to draw any definitive conclusions based on this retrospective heterogeneous data.

Izmirly and colleagues retrospectively identified 325 cases of cardiac NL from the US-based Research Registry for Neonatal Lupus with documentation of maternal anti-SSA/Ro and/or anti-SSB/La antibodies, excluding those with isolated first-degree AV block or sinus bradycardia. Of these, nearly 18% died; 30% of these were in utero demises. A multivariate analysis of outcomes revealed that an increase in mortality correlated with hydrops fetalis, endocardial fibroelastosis (EFE), maternal diagnosis of SLE or SS, diagnosis early in gestation, and a low ventricular rate. Advanced AV block without associated signs of myocardial involvement carried a mortality rate of \( \approx 8\% \); however, if the fetus concomitantly had EFE or a dilated cardiomyopathy, the mortality rate increased to 42% and 37%, respectively. There was 100% mortality in the 9 cases in which advanced AV block, EFE, and dilated cardiomyopathy were all present. An increased risk of in utero mortality was also associated with the maternal administration of fluorinated steroids and/or terbutaline. Unexpectedly, compared with whites there was an increased rate of hydrops fetalis and EFE in the children born to black, Hispanic, Asian, and mixed-race women, which correlated with an increased mortality rate. By 1 year of age, \( \approx 50\% \) of these children underwent pacemaker implantation, and by ten years of age, 70% had received permanent pacemakers.

In the current issue of *Circulation*, both Eliasson et al and Izmirly et al demonstrate similar risk factors for an increased mortality in cardiac NL, including associated hydrops fetalis, diagnosis early in gestation, a low ventricular rate, and evidence of myocardial involvement. Interestingly, Izmirly et al also note an increased risk of in utero mortality associated with maternal steroid administration. They theorize that this is not a directly causal relationship, but instead a result of such medications being used only in the most severely affected fetuses. However, this may be falsely reassuring; as noted in Eliasson et al, there is an unexpected lack of correlation between ultrasound markers of fetal wellness and maternal steroid administration. Another predictor of in utero demise was an early gestational age at initial diagnosis, which Izmirly et al believed suggested an earlier and consequently more extensive damage to the developing heart. However, any correlation between gestational age at diagnosis and incidence of cardiomyopathy, EFE, or valvular disease was not demonstrated in their report.

Given that maternal glucocorticoid administration is not without risk to both mother and fetus, and that the benefits of such therapy remain unclear, clinicians may need to consider a more systemic, objective method of risk stratifying women before deciding on the appropriateness of universal transplantation steroid therapy for advanced AV block in the fetus. Such objective measures could include the biophysical profile score and cardiovascular profile score as standardized methods of quantifying fetal cardiac wellness. If the timing and effectiveness of maternal steroid administration remains unclear, such evaluations of fetal wellness may ultimately play an important role in determining the value of early fetal delivery. Although premature delivery obviously carries risk and has specifically been shown to be associated with increased mortality in anti-SSA/Ro-exposed neonates, it remains the only way to truly end exposure of the fetal myocardium to damaging maternal antibodies.

Though rare, the cardiac manifestations of NL are severe and can be associated with significant morbidity and mortality. As reported in 2 studies in the current issue of *Circulation* and prior studies aimed at evaluating mortality or the effectiveness of maternal steroid administration, there is wide variation relative to maternal antibody status, documentation of AV block diagnosis, cohort size, and details of glucocorticoid treatment strategies. To thoroughly evaluate management and treatment strategies of an uncommon but clinically important disease, large, prospective, multi-institutional trials are still needed but realistically may not be feasible. Analogous to the hotly contested debates by the interns contemplating steroid treatment for the Yellow Man in *The House of God*, the clinical risk/benefit considerations, timing, dose, and therapeutic value of corticosteroids remain unknown. Psychologically, to the caregiver, a trial of empirical treatment often feels better than watchful waiting. But even now, with 2 relatively large sample sizes in the current retrospective multicenter reports published in this issue of *Circulation*, it remains uncertain whether maternal steroid administration provides therapeutic benefit to fetuses with antibody-associated heart block. It seems that transplacental maternal steroid treatment after the autoantibodies have already taken their toll on the developing fetal myocardium and conduction system might be too little, too late. The question remains unanswered as to whether there may be benefit in a select
group of patients with early disease, specific antibody or genetic factors, or some other features yet to be identified.

**Disclosures**

None.

**References**


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